TRANSPERFECT
TRANSLATIONS

AFFIDAVIT OF ACCURACY

I, Tyler Mickelson, hereby certify that the following is, to the best of my knowledge and belief, a true and accurate translation of the accompanying Patent from German into English.

ATLANTA
BOSTON
BRUSSELS
CHICAGO
DALLAS
DENVER
FRANKFURT
GENEVA
HONG KONG
HOUSTON
LONDON
LOS ANGELES
MIAMI
MINNEAPOLIS
MONTREAL
MUNICH
NEW YORK
PARIS
PHILADELPHIA
RESEARCH TRIANGLE PARK
SAN DIEGO
SAN FRANCISCO
SEATTLE
STOCKHOLM
TOKYO
WASHINGTON, DC

Tyler Mickelson
TransPerfect Translations, Inc.
601 Thirteenth Street, NW
Suite 320 North
Washington, DC 20005

Sworn to before me this
30th day of October 2006

Signature, Notary Public

Lisa Sherfinski
Notary Public, District of Columbia
My Commission Expires 01-01-2008

Stamp, Notary Public

Washington, DC

Optical Biopsy Instrument

The invention relates to an optical biopsy instrument suitable for taking tissue samples from small duct systems, especially milk ducts from the breast, and a method for taking tissue samples using the biopsy instrument.

Breast cancer is the most common cause of death due to cancer in women in Germany, accounting for approximately 20% of the cancer mortality, and thus constitutes a substantial medical and socioeconomic problem. Early detection is enormously important for a favorable prognosis and successful treatment of breast cancer. It has thus been shown in international studies that a significant reduction in breast cancer mortality can be achieved by early detection programs with (radiological) mammography screening.

However, in recent years there has been a definite increase in intraductal carcinomas, i.e., carcinomas of the mammary milk ducts (ductus lactiferi), from 4% to more than 20% (Bässler, Onkologie 4, 1998, 878–895). Therefore, these milk duct tumors are currently at the center of efforts to improve the diagnosis and treatment of breast cancer. However, early diagnosis of small tumors is problematical because of their property of propagating slowly in the preformed mammary duct system, and conventional radiological methods (mammography) or ultrasound (mammary sonography) are often inadequate in detection. The clinical symptoms and mammographic findings lead to a diagnosis in only 40% to 60% of patients (Bässler, Onkologie 4, 1998, 878–895).

Endoscopic examination of the mammary milk ducts, a so-called ductoscopy, could improve the efficacy of early detection of intraductal carcinomas in particular. For a long time, however, this has been impossible because of the small cross section of the duct. Only through miniaturization of endoscopes has direct optical examination of these small duct systems become possible. In contrast with other organs however so far there has been little experience in microendoscopy of the milk ducts, whereby these studies have been performed for localization of intraductal papillomas or for other purposes (e.g., Shen et al., Am. Cancer Soc. 89, 2000, 1512–1519; Okazaki et al., Eur. Radiol. 9, 1999, 583–590; Love and Barsky, Lancet 348, 1996, 997–999; Rimbach et al., Zentralbl. Gynakol. 117, 1995, 198–203; Okazaki et al., Jpn. J. Clin. Oncol. 21, 1991, 188–193). However most of these methods do not allow tissue samples to be taken but at most allow epithelial cells to be obtained by lavage of the duct. If there is the possibility of a biopsy, it is performed blindly and without visible monitoring. However, it is precisely an accurate visually controlled biopsy option that is urgently needed for optimized diagnosis of dissemination to improve therapeutic planning and results and also with regard to treatment that preserves breast tissue in breast cancer.

Shen et al. (Surg. Endosc. 15, 2001, 1340–1345) describe a biopsy method for milk ducts in which a fiber endoscope with a traditional thin biopsy cannula attached to the end is inserted into the milk duct with visual monitoring, then the endoscope is removed and tissue is aspirated through a very thin syringe that is introduced. However, the problem here again is that the actual biopsy is not performed with visual monitoring. This leads to the risk of biopsy of the wrong tissue, because even an extremely small deviation from the selected biopsy site can lead to an unreliable diagnosis.

Other publications have described biopsy instruments for other purposes which also have no direct endoscopic monitoring of sampling. US Patent 4,651,753 describes a biopsy instrument that is intended for use in conjunction with an endoscope. The biopsy instrument comprises essentially a cylindrical outer sleeve with a lateral oval opening through which a flexible cutting cannula which is arranged coaxially in the outer shell and is movable axially, carrying a cutting blade on its distal end, and a pusher tube arranged coaxially in the cutting channel. Tissue is sampled by guiding the instrument through an endoscope to the relevant biopsy site, drawing a tissue sample that is to be taken by means of a vacuum then generated through the lateral opening into the interior of the instrument and severing it by advancing the cutting cannula and then conveying it with the pusher tube into a distal chamber of the outer cylinder. One disadvantage of this instrument is the complicated design which impedes miniaturization, which is required for use in milk ducts, for example. Furthermore, direct endoscopic observation of the biopsy procedure is impossible. A similar principle which therefore has the same disadvantages is described in US Patent 5,526,822.

US 01/0047183 A discloses a biopsy instrument comprising a double cannula whereby the two parallel cannula lumens (working channel and vacuum channel) are interconnected through vacuum holes. To take a biopsy, tissue is drawn by vacuum through an opening arranged in the side of the working channel and is severed with the help of a tubular rotating cutting tube that is axially movable in the working channel. Here again, as in US Patent 4,651,753, it is impossible to take a biopsy with endoscopic observation.

In summary, it can be concluded that the clinical benefit of the promising technique of ductoscopy has been enormously limited by the low optical quality in the past, the lack of a working channel in currently available instruments and especially the lack of possibility of performing a biopsy with visual supervision. This is currently preventing clinical acceptance and widespread use of this method.

Therefore, the object of the present invention has been to make available a biopsy instrument that will allow biopsies to be taken with direct visual monitoring even in extremely small cavities, in particular in milk ducts in the breasts.

According to this invention this object is achieved by an optical biopsy instrument that has the features of Claim 1. The inventive biopsy instrument comprises

(a) an essentially cylindrical cannula having a proximal end and a distal end whereby the cannula has at least one lateral opening and

(b) an endoscope that is axially movable within the cannula.

Thus the instrument is characterized by a very simple design which allows for the first time direct endoscopically monitored sampling through the lateral opening in the cannula even in very small vessels or duct systems, especially in the milk ducts of the breast. This avoids frequent sources of error with the biopsies that were previously performed as blind biopsies.

Separation of the tissue sample to be taken from the remaining tissue is preferably simplified by the fact that the at least one lateral opening in the cannula has in at least some areas a cutting area on its circumference facing the distal end and/or on its circumference facing the proximal end. In this way the tissue sample can be severed easily by a suitable movement of the cannula and the endoscope in relation to one another by moving only the cannula. These procedures are explained in detail below.

The cutting area of the lateral opening may advantageously be implemented by a ground and polished section of the circumference of the opening and/or by teeth on the circumference. A combination of teeth and a polished section is also conceivable. The opening itself may have an essentially round, oval, elliptical or rectangular shape, for example.

According to an advantageous embodiment of the invention, an outside diameter of the endoscope corresponds essentially to an inside diameter of the cannula or is slightly smaller than the latter, i.e., the play between these two components is minimal. Such a relative dimensioning of the cooperating components in relation to one another facilitates the cutting on the one hand while on the other hand making it easier to generate a vacuum in the cannula space, which is additionally facilitated by the fact that the cannula is sealed on its distal end with a wall which is preferably transparent.

The endoscope may optionally be a rigid or flexible endoscope, i.e., both mirror endoscopy and glass fiber endoscopy may be used. However, the rigid endoscope has proven to be especially advantageous because of its easier handling in cutting.

Various procedures for taking tissue samples of duct systems using the inventive biopsy instrument are conceivable.

According to a first variant

(a) an optical biopsy instrument comprising
- an essentially cylindrical cannula having a proximal end and a distal end and having at least one lateral opening and
- an endoscope that is axially movable in the cannula,

is inserted into the duct up to a biopsy site with endoscopic monitoring,

(b) the tissue sample is brought to an interior of the cannula through the open opening and

(c) the tissue sample is severed from the remaining tissue by advancing the endoscope beyond the lateral opening and/or retracting the cannula until the lateral opening is closed.

According to this first variant, the tissue sample is thus severed by pushing the cannula and the endoscope toward one another, so that the tissue sample is severed by a pressure exerted by the endoscope against the cutting area of the opening.

According to a second variant, when the endoscope is retracted, the cannula is at the same time used as a planing tool to bring about the severing of the tissue sample when the opening is exposed. To so do

(a) the optical biopsy instrument described above is inserted into the duct with endoscopic monitoring until the lateral opening comes to lie over the biopsy site and

(b) the tissue sample is brought into an interior of the cannula through the open opening and

(c) the tissue sample is severed from the remaining tissue by advancing or retracting the cannula together with the attached endoscope with the lateral opening exposed, while exerting a slight manual pressure against the tissue sample.

Additional preferred embodiments of the invention are derived from the other features characterized in the subclaims.

The invention is explained in greater detail below in an exemplary embodiment on the basis of the respective drawings, in which

Figure 1	shows a microendoscopic system consisting of an endoscope, a video handle and a light source,
Figure 2	shows a perspective side view of an inventive cannula,
Figures 3a through 3f	show side views of inventive cannulas with different designs of the opening and its cutting areas,

Figures 4a through 4d steps of an inventive method for biopsying a tissue sample according to a first variant and

Figures 5a through 5d steps of an inventive method for biopsying a tissue sample according to a second variant.

Figure 1 gives an overview of a microendoscopic system like that used in the present invention. The system comprises an endoscope 10 (ductoscope) which is suitable for endoscopy of tight channels, especially the milk ducts of the breast (ductus lactiferi) because of its very small dimensions. This is a rigid endoscope (from the company Volpi AG in Switzerland) with an outside diameter ⌀ of 1 mm and a length L of 6 cm. The endoscope is based on the so-called gradient index technique (GRIN) and permits a much higher optical resolution and better brightness yield in comparison with fiber-optic endoscopes.

The system also comprises a light source 12, e.g., a metal halide light source. A fiber-optic cable 14 and a camera cable 16 leading to a video handle 18 can be connected to the light source 12. The video handle 18 has a camera head (not shown in detail here) which includes a CCD camera which has a resolution of 625 lines and a manual focus (2 mm – ∞). The CCD camera supplies a digital video signal of excellent quality. The endoscope 10 can be connected to the video handle 18 via a connection head 20 and thus the endoscope can be connected to the light source 12 via the fiber-optic cable 14 and the camera cable 16.

From the standpoint of its good optical properties and its simple maneuverability, this system is suitable for widespread clinical use. Although the endoscope has a working channel through which lavage can be performed, for example, the small diameter does not allow a biopsy. This problem is solved according to this invention by using a cannula 22 that is attached to the endoscope 10 as shown in Figure 2.

The cannula 22, which essentially has the shape of a hollow cylinder, has a proximal end 24 and a distal end 26. The cannula may be made of a rigid plastic or metal, for example. Its inside diameter is preferably chosen to be slightly larger than the outside diameter of the endoscope 10 so that there is only a small amount of play between the endoscope 10 and the cannula 22 attached to it. In the concrete case, a cannula 22 with an outside diameter of 1.2 mm was used. The cannula 22 has a lateral opening 28 near the tip of the cannula, i.e., in the area of its distal end 26, said opening being furnished in at least some areas with a cutting area 30.

Figures 3a through 3f illustrate several exemplary embodiments of the cannulas 22 which differ with regard to the design of the lateral opening 28 and the type of cutting area 30. The openings 28 according to figures a, b, d and e have an essentially oval shape whereas the openings 28 according to figures c and f are mostly rectangular in shape. Other shapes of the opening 28 that

are not shown here, e.g., with a round or elliptical contour are also conceivable. Likewise more than one lateral opening 28, e.g., two openings 28 opposite one another may also be provided.

The three variants (3a through 3c) illustrated in the figure above have cutting areas 30 only on the area of the opening 28 facing the distal end 26 of the cannula 22. The lower three variants (3d through 3f) however also have cutting areas 30' on the area of the opening 28 facing the proximal end 24 of the cannula 22. A peripheral cutting area over the entire circumference of the opening 28 is also conceivable or for certain manipulations of the biopsy instrument only cutting areas 30' may be provided on the proximal end.

In the variants 3a and 3d, the cutting areas 30, 30' are implemented in the form of a polished section of the cannulas 22 (indicated by bold lines). On the other end, the cutting areas 30, 30' of the other variants consist of teeth, whereby the cutting areas 30, 30' of variants 3b and 3e are each designed in the form of a single tooth and variants 3c and 3f are each designed in the form of multiple finer teeth. In addition, it may also be advantageous to combine teeth with the polished section.

Two different methods of performing a biopsy of a tissue specimen using the inventive biopsy instrument are thus depicted schematically in Figures 4 and 5.

According to the first method diagramed in Figure 4, the biopsy instrument, labeled as 100 on the hole and consisting of the endoscope 10 and the cannula 22 attached to the former is inserted with visual endoscopic monitoring into a hollow vessel that is to be examined (not shown here), in particular into a milk duct (Figure 4a). In this phase the endoscope 10 is preferably in a maximally advanced position inside the cannula 22 so that the distal tip of the cannula essentially seals the tip of the endoscope 10. For better handling, the cannula 22 has a handle 32 in its proximal area 24. As soon as a tissue sample 34 that is to be removed enters the visible area of the endoscope 10, the insertion movement of the instrument 100 is terminated.

Then the cannula 22 is advanced with a handle until the opening 28 and the cannula 22 is exposed, i.e., it is no longer sealed by the endoscope 10 on the inside and the opening 28 comes to lie above the tissue sample 34 (Figure 4b).

In the next step the tissue sample 34 that is to be removed is pulled through the opening 28 into the interior of the cannula 22 (Figure 4c). This may take place spontaneously due to a tissue tension that acts against the cannula 22 and the opening 28. Optionally the penetration of tissue can be supported by a slight vacuum created in the cannula 22 in which case the vacuum can be created by the previous advance of the cannula 22. In this case the distal tip of the cannula may be sealed with a transparent wall (not shown). Optionally the vacuum can also be created through the working channel of the endoscope 10.

As soon as the tissue sample 34 has penetrated into the cannula, it is severed from the remaining tissue by advancing the endoscope 10 or retracting the cannula 22. It is also advantageously possible to combine the two movements by moving the cannula 22 and the endoscope 10 toward one another (see arrows in Figure 4c). Because of the shearing effect of the cutting area 30 of the opening 28 of the cannula 22, the tissue is clamped and severed, so that the severed tissue sample 34' is pushed into the interior of the distal area 26 of the cannula 22 (Figure 4d). Then the entire biopsy instrument 100 together with the tissue sample 34' can be removed from the duct system. The closure of the cannula tip by a window may also be advantageous here to prevent a loss of the tissue sample 34' in extracting the instrument 100.

Figure 5 shows a second variant of the method for biopsy of a tissue sample. Insertion of the biopsy instrument 100 (Figure 5a) and introduction of the tissue sample 34 (Figures 5b and 5c) take place by analogy with the method described previously in conjunction with Figure 4. The difference here is in the method of severing the tissue sample 34, which is accomplished by a planing tool-like use of the cannula 22. To do so, as soon as the tissue sample 34 has penetrated into the cannula 22, the entire instrument 100 consisting of the cannula 22 and the endoscope 10 attached securely thereto is moved in a common direction (see arrows in Figure 5c) toward the tissue sample 34 by exerting a slight manual pressure against the tissue sample 34, so that the cutting area 30 of the cannula 22 acts on the tissue sample 34 and severs it (Figure 5d). Depending on whether the cutting area 30 is situated on the distal or proximal end of the opening 28, the severing movement in the same direction may take place in one direction or the other. In the example depicted here where the cutting area 30 is arranged on the distal end of the opening 28, the tissue is severed by retracting the instrument 100.

For another biopsy procedure (not shown here), a second lateral opening in the cannula 22 is advantageous. Then with the endoscope 10 retracted, the cannula 22 is pressed with a lever movement onto the tissue sample 34 to be removed so that the tissue penetrates through the first lateral opening 28 into the interior of the cannula and partially comes out of the cannula 22 again into the ductus through the second opening on the opposite side. The sample 34 has been severed either by moving the endoscope 10 and the cannula 22 toward one another according to Figure 4 or by a lever-like use of the instrument 100 according to Figure 5. A cutting area 30 on the second lateral opening is not absolutely necessary for this variant.

The entire process of taking a sample according to all the methods described here may be monitored and controlled under optimum endoscopic monitoring. In particular the removal site can be approached in a very targeted manner by means of the inventive biopsy instrument 100. Faulty samples which were previously common in a blind biopsy due to missing the biopsy site by a minor amount are not avoided.

Because of the great medical and socioeconomic relevance of breast cancer, it must be assumed that the inventive biopsy instrument and the methods of using this method will find great acceptance among physician and patients. This method is simple and inexpensive and can be used after only a short training of the physician accordingly. The biopsy instrument is a low cost product so it may be used in clinics as well as in the area of individual medical practices.

REFERENCE NUMERALS

10	Endoscope
12	Light source
14	Fiber-optic cable
16	Camera cable
18	Video handle with camera head
20	Connecting head
22	Cannula
24	Proximal end
26	Distal end
28	Opening
30	Cutting area
32	Handle
34	Tissue sample